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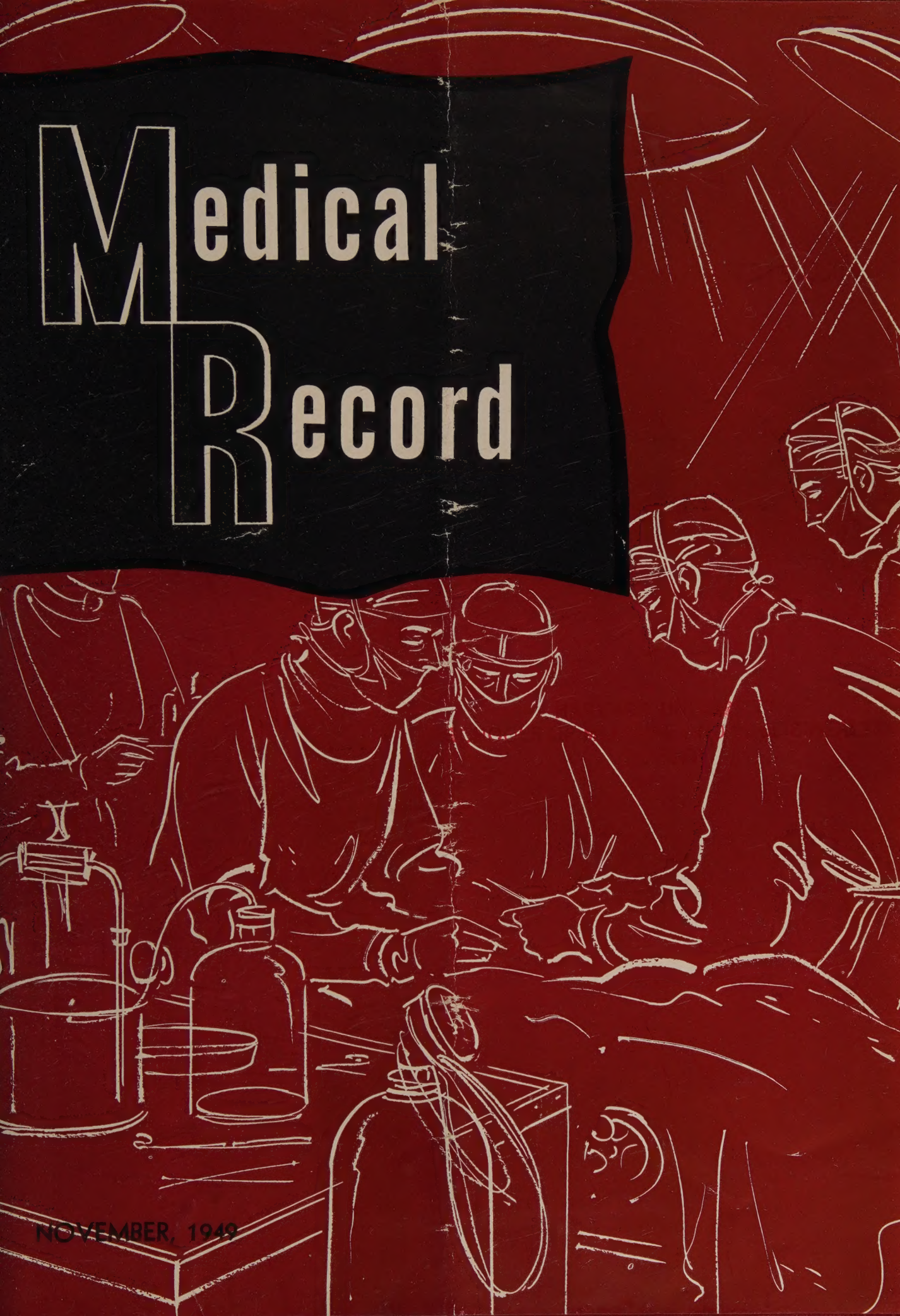

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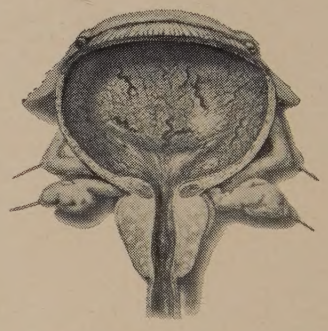

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VOL. 162, NO. 11 NOVEMBER, 1949 WHOLE NO. 2801

FURTHER CONCEPTS OF DICUMAROL IN ACUTE CORONARY OCCLUSION

GEORGE SCHWARTZ, M. D.
New York 16, N. Y.

The purpose of a previous paper was to briefly portray the historical data associated with the origin of dicumarol, the animal and human experiments which initiated its utilization in the human afflicted with an acute coronary episode, the methods of administration commonly employed, the methods utilized to obviate the one serious complication of hemorrhage, and to acknowledge the present timidity in its total utilization in acute coronary episodes, and finally, present a theory and cite cases in which dicumarol might have been utilized prophylactically in minimal (100 mg.) doses daily without deleterious effect—perchance with an advantageous effect—and without the aid of the laboratory.

Relative to the historical review including the visualization and cognizance of a peculiar phenomenon among cattle, relative to the keen observations of both Schofield and Roderick and to Roderick's monograph entitled "The Pathology of Sweet Clover Disease in Cattle," relative to the isolation and synthesis of the hemorrhagic compound as a result of the brilliant activities of Professor Link and his associates of the Wisconsin Agricultural Experimental Station in 1941, relative to the discarding of "dicoumarin" and the acceptance of "dicumarol," relative to the animal experimentation performed by Blumgart and his associates and by Beattie and his associates; relative to the clinical evaluation by Glueck and his associates, by Wright, by Nichol and Page, by Peters, Guyther and Branbel and by Allen and his associates; relative to the techniques employed and the modifications of the original Quick method as utilized by Wright and the Mayo Clinic; relative to the Russel viper venom modification, relative to the action and contraindications of dicumarol; for all these I respectfully invite attention to my contribution published in the *New York Physician*, Vol. 31, No. 4, November 1948. Further an extensive bibliography of 30 sources are included.

The material outlined above could readily serve as an insight into a problem which was perplexing for a period of time; however more observations and investigations are daily events and thus, though despite the fact that heparin and dicumarol are not ideal anti-coagulants they will serve admirably until a future moment of unique achievement in anti-coagulant therapy.

However despite recent additions to the literature, to which I shall allude, the two fundamental questions stressed in my original dissertation remain as yet unanswered and until results prove otherwise I shall continue to investigate in the fashion described. The discussion relative to these questions and the description of the first eight cases are hereby included as previously published. Quoting from *The New York Physician:* Two Questions Inferred: Of what significance is the lag period of some 24 to 72 hours in which the patient remains unprotected from possible thrombosis due to lack of inadequate though progressive development of hypoprothrombinemia? Levan (1) states that statistical evidence demonstrates that for some unknown reason, this theoretical justified criticism is not a factual threat. At any rate if rapid anticoagulation is desired and when immediate reliable laboratory determination of the value for prothrombin in the blood is not practical, heparin may be utilized to complement the action of dicumarol. Heparin may simply and safely be

administered by repeated intravenous injections of 50 mg. in five cc. every four hours, or of 100 mg. in 10 cc. every six hours. This method is effective and the coagulation time need not be tested. It acts rapidly and its action terminates within a few hours after its usage ceases. Any possible untoward hemorrhage is as easily controlled with the administration of fresh blood or vitamin K as previously described.

"The second and more significant question, because of its implications, arises. It has been stated by varied authors that the value of the routine use of dicumarol in all cases of coronary thrombosis has been considered and questioned and the major portion of the material published to date does not justify the conclusion that dicumarol will affect the results in uncomplicated cases of coronary thrombosis. The implications now present themselves. Shall we withhold the administration of that valuable addition to our armamentarium until such time as complications arise and only then utilize it? Shall dicumarol be utilized prophylactically? In what dosage? Have we any data available, no matter how slight the case load? Is there any experimental evidence which would imply a contraindication? Is the method of trial and error justified in this instance?

"It is indeed possible that sufficient animal experimentation exists (as briefly described above in the two series of Blumgart et al (2), and Beattie et al (3) to definitely warrant the conclusion that dicumarol produces no adverse effect upon the myocardium. Thus its utilization is not contraindicated in so far as the myocardium is concerned.

"I have not discovered any reference in the literature, or from the experience of my colleagues or from my own cases that minimal daily dosages of 100 mg. of dicumarol have ever resulted in hemorrhagic episodes.

"In view of the fact that were spontaneous hemorrhage to occur through the utilization of even minimal doses of dicumarol, and that that effect could easily be controlled by either the intravenous administration of synthetic vitamin K as described above or by the transfusion of fresh whole or fresh whole citrated blood, and in view of the fact that in multitudinous areas of this country adequate laboratory facilities are unavailable or entirely non-existent, the concept arose as to whether or not by trial and error we might conceivably arrive at a dosage which would be relatively sound and perhaps entirely harmless and yet accord a measure of prophylactic value. Perchance that measure of prophylactic value would actually serve beneficially in locales and situations where laboratory facilities were nil.

"Though cognizant of any possible criticism, I endeavored, in the few cases cited below, to most critically observe these patients for any untoward sign or symptom, or any maifestation of spontaneous bleeding no matter how slight. Six patients were hospitalized and two confined to their homes; however in one instance, the referring physician insisted upon blood levels at stated periods.

"In the eight cases cited below, all were electrocardiographically verified as acute coronary episodes, seven of which suffered their first occlusion and one of which suffered his second occlusion. The moment the diagnosis was established clinically, 100 mg. of dicumarol was administered in each case together with morphine, atropine, the xanthine derivatives, oxygen, etc. Together with the usual conservative therapy employed, 100 mg. of dicumarol was administered daily until a few days prior to discharge and no routine blood levels with the exception noted above, were accomplished. All eight cases made or are making splendid uneventful recoveries.

"It would be untenable to maintain and dogmatically proclaim that the procedure just described was wholly responsible for the vital statistics. Yet though but eight cases are involved, the thought projects itself as to whether or not small doses of dicumarol may prove effective, may more or less entirely remove the hazards associated with the administration of larger dosages of dicumarol and may the more readily be utilized when the accepted standards of a laboratory are unavailable.

"*First Case:* Male, aged 38, suffered his second coronary occlusion. Hospitalized and received conservative therapy including 100 mg. of dicumarol daily until a few days prior to discharge. Infrequent blood levels were insisted upon. Eight months following the acute episode there was a 0.5 cm. increase in the transverse diameter of the heart, with a bulge of the left ventricle which conceivably will eventuate into an aneurysmal dilatation.

"*Second Case:* Male, aged 47, suffered his first acute coronary episode. In addition to morphine and atropine, the xanthine derivatives and aminophyllin were employed. A terrific itchy and reddish pin-point rash developed. Papaverine hydrochloride was substituted and when the above phenomena was alleviated, the original medication was re-introduced only to indicate the same state. Papaverine was then utilized exclusively. Aside from this untoward state, no other adverse signs or symptoms presented themselves during the entire hospital period and 100 mg. of dicumarol was utilized continually.

"*Third Case:* Female, aged 42, suffered her first occlusion and was confined to her home. After a two week period of absolute bed rest, she was permitted to be brought to the office for electrocardiography and then returned home to bed confinement. Little physical energy was employed. This process was repeated for four weeks. One hundred mg. of dicumarol was administered daily. No untoward effect was noted. The electrocardiogram manifests but mild myocardial damage and the measured transverse diameter of the heart remains less than the predicted diameter for age, weight and height.

"*Fourth Case:* Male, aged 50, suffered his first occlusion and confined to his home after one week of hospitalization. The patient left the ward for personal reasons and his referring physician was unable to continue. The patient was a distinct alcoholic, when well and able periodically became incapacitated because of alcoholic imbibition. For the five week period of home and bed confinement

he received papaverine and 100 mg. of dicumarol daily. No untoward effect was noted. Recovery was distinctly uneventful though the final electrocardiogram manifested extensive myocardial damage. Since the patient's return to his usual labors, he has again indulged excessively in alcohol.

"*Fifth Case:* Female, aged 56, suffered her first acute episode of the coronary vascular tree. She had oft-times been subjected to the anginal syndrome. No untoward effect noted throughout her hospital stay during which she received 100 mg. of dicumarol daily. Her electrocardiographic study reveals moderate residual myocardial damage. Following hospitalization she has experienced repeated severe angenoid seizures but no further occlusion.

"*Sixth Case:* Male, aged 54, suffered his first acute coronary episode and as of 9/14/48 has been hospitalized for a period of three weeks. The usual conservative therapy has been employed with 100 mg. of dicumarol daily. No untoward effects noted.

"*Seventh Case:* Male, aged 60, suffered his first coronary occlusion during the recent heat wave and while working as a waiter. As of 9/14/48 he has been hospitalized for two weeks receiving 100 mg. of dicumarol daily. No blood levels have been sought.

"*Eighth Case:* Female, age 51, presented a history of two weeks to three weeks duration in which she suddenly was seized with sharp precordial pain which disappeared in a reasonable period of time. However because of transient recurrence of the precordial distress, she was electrocardiographed and a recent acute anterior coronary occlusion was diagnosed. The patient was entirely ambulatory during that period of time accomplishing all her household duties, etc. She was then confined to bed at home for a period of a week and then because of the usual problems was hospitalized where as of 9/19/48 she has been receiving 100 mg. of dicumarol daily together with the usual conservative therapy. No untoward subjective or objective findings.

"In brief, because of the non-deleterious effect of dicumarol upon the myocardium and because of its easily controllable complication of hemorrhage, and because of the temerity in its possible usage away from laboratory advantages, and because of its conceivable prophylactic advantages, dicumarol was utilized in 100 mg. doses in the last eight cases of this writer, to vaguely ascertain its possible routine utilization in any instance of an acute coronary episode.

"In the eight cases cited, no untoward or hazardous effect was noted, and the first five cases made splendid uneventful recoveries. The last three cases are still hospitalized and similarly manifest no unusual findings.

"It is thus suggested that especially in areas where adequate laboratory facilities are unavailable, that the physician utilize daily 100 mg. of dicumarol in all cases of acute coronary occlusion for its possible prophylactic advantage."

Since the above was published, more opportunity has naturally presented itself for further evaluation of our thought concepts relative to anti-coagulant therapy in regard to the utilization of dicumarol. Following the discharge of case No. 6 after seven weeks of hospitalization, the urine was noted to be discolored into a reddish hue, laboratory procedures elicited the presence of an appreciable number of red cells. The patient was carefully observed and within 36 hours the hemorrhage ceased spontaneously and at this writing no other untoward effect was noted. The patient has returned to all of his previous mental and physical activities and there is no clinical or laboratory evidence of further deleterious effect. The patient merely receives papaverine hydrochloride grains 1½, t. i. d.

Case No. 10, a physician's brother, similarly suffered bladder mucosal hemorrhage which was curbed as described below. However in view of the first significant mal-effect of utilizing 100 mg. of dicumarol daily in case No. 6, the obvious thought concept that even at the levels of administration employed, that perhaps a cumulative effect had occurred and that perhaps the prothrombin time had been elevated above 50 seconds, or that the prothrombin level dropped below 10 per cent of normal, a modified administration of dicumarol was contemplated; and it was then decided to administer 100 mg. daily for the first three weeks and then reduce the quantity to 75 mg. daily for the next week and conclude by reducing the dosage to 50 mg. daily for the remainder of the hospital confinement.

The rationale for this concept, if it may be considered rationale, has been stressed both in this paper and my previous publication. One may infer the same from an article recently published by Wright and his associates (4) in the *American Heart Journal*, December 1948, in which he states, "Although the minimum prolongation of the prothrombin time necessary to obtain a therapeutic effect from Dicumarol in each patient has not been established, it is our experience that a range of from 30 to 50 seconds, as measured by the Link-Shapiro modification of the Quick onestage technique, produces a safe and effective therapeutic level. This range of prothrombin time approximates a decrease in prothrombin activity to between 20 and 10 per cent as determined in our laboratory."

I express the thought that perhaps laboratory levels are not the fundamental criteria to produce the desired effect of that level of anticoagulation which will best protect the patient from hemorrhagic manifestations. And I again stress that those who find themselves unequipped with the necessary laboratory technique and technicians and material, those who practise in isolated areas, these require other safe approaches to this intriguing problem.

An analogy by no means a truism, but merely to serve as a vehicle for possible analysis, the administration of one unit (1½ grains of digitalis or 0.1 mg. of a digitoxin) may over a period of time cause a ventricular response of 90 per minute in a case of auricular fibrillation; the administration of 1½ units may result in a ventricular response of 80 per minute; the administration of two units daily may cause a resultant 70 response. Should

there be, in all three instances cited, no evidence clinically of congestive failure, nausea, diarrhea, etc., who, logically, may state which level of ventricular response is the most advantageous? Normal hearts function between 60 and 100 contractions per minute. There is no concrete evidence that the prothrombin time necessary to obtain a therapeutic effect must attain the 30 second level. Perhaps beneficial results are obtained at a lesser level, a level too sensitive for our present laboratory procedures.

Further cases are now cited—although it is admitted that the case load in so far as numbers are concerned are definitely few in comparison to studies recorded in the literature.

Case No. 9, male, aged 50, suffered his first coronary occlusion, received the usual conservative therapy and 100 mg. of dicumarol daily for his six week period of hospitalization and enjoyed an uneventful hospital course.

Case No. 10, male, aged 46, suffered his first coronary occlusion. This engineer, a physician's brother, suffered precordial distress while climbing in and out of excavations, was brought to the office, the diagnosis was established, was confined to his bed at home for a period of approximately six weeks. The usual therapy was instigated together with the dicumarol of 100 mg. dosage daily. Towards the close of his six weeks hemorrhagic manifestations were noted by the appearance of reddish hued urine which proved to be a discoloration due to red blood cells. Four doses of 40 mg. of synthetic vitamin K were administered, the first two intravenously and the second two intramuscularly. The patient's brother suggested oral administration as well and thus vitamin K was administered orally. The hemorrhagic manifestations ceased shortly after its inception and though this episode occurred months ago, no pertinent abnormality exists today.

Case No. 11: This case is included merely to emphasize that coronary deaths occur even in this series. This male, aged over 60, had been desperately ill for some six days and was confined to a hospital. The electrocardiographic examinations disclosed a terrifically bizarre graphic picture of tremendous myocardial damage. The heart sounds were rather imperceptible, the state of shock was unusual, oxygen therapy, etc., had been employed. Serial electrocardiography manifested no real graphic changes in the course of an acute occlusive state. Dicumarol was instigated. An exitus occurred on the tenth day and clinically appeared to be the result of spontaneous rupture of the myocardium.

Case No. 12, male, aged 56. Suffered his first coronary occlusion, was seen at home, the usual medication and 100 mg. of dicumarol was instigated. Two days later he was hospitalized. After three weeks, the dicumarol was decreased to 75 mg. daily, after the fourth week until the close of the sixth week 50 mg. were administered daily. Towards the close of the sixth week the patient developed lobar pneumonia which responded dramatically to chemotherapy. Following discharge and at this writing several weeks have intervened and no untoward mal-effect has been noted.

Case No. 13, male, age 52. With the routine described above, this individual who suffered his first occlusive state, enjoyed an uneventful hospital course of five and a half weeks.

Case No. 14, male, aged 48. Received the original routine relative to dicumarol therapy for a period of three weeks in addition to conservative therapy. The referring physician was hesitant to permit further dicumarolization after the prothrombin time level attained 33 seconds, the examination being performed at his insistence. Dicumarol was then discontinued. At any rate throughout the hospital course no deleterious effect was noted.

Case No. 15, female, aged 67, a physician's mother, suffered her first anterior coronary occlusive state and was immediately hospitalized. This instance was characterized by a moderate degree of congestive heart failure, more than moderate cyanosis and dyspnoea. Oxygen therapy was required for a prolonged period of time and the usual routine was employed. Morphine, atropine, aminophylline were administered. Dicumarol was administered originally in 100 mg. tablets daily, then reduced to 75, and finally, the last three weeks of hospitalization but 50 mg. were administered daily. Aside from the partially resistent congestive heart failure, the recovery was uneventful.

Case No. 16, male, aged 53, was diagnosed as an acute anterior coronary occlusive state at his residence and immediately was hospitalized. Marked cyanosis, dyspnoea and orthopnea characterized this case. The clinical course was rather hectic for the first week of bed confinement. Therapy as described above was employed and thereafter the clinical course and recovery proved uneventful.

Case No. 17, female, aged 75, suffered her first coronary occlusive state which electrocardiographically proved to be a posterior coronary occlusion. The usual therapy as described was employed and the six week clinical course at the hospital was most benign in character.

Case No. 18, male, aged 76, was immediately hospitalized following the advent of somewhat severe subjective distress, and electrocardiographic studies disclosed not only the occlusive state, but also marked left bundle branch block together with nodal rhythm. A normal sinus rhythm and elimination of the conduction block eventually occurred, and the further clinical course at the hospital was uneventful. The usual therapeutic routine was employed.

Case No. 19, female, aged 68, was hospitalized and the graphic picturization stigmatized this myocardium as one subjected to the acute posterior coronary occlusive state. The usual routine of vaso-dilation and sedation was employed but relative to dicumarol therapy, because of the small stature of the patient—and this thought may be questioned—but 100 mg. were administered for three days and thereafter 50 mg. were administered daily for the six week hospital period. The recovery was uneventful.

Case No. 20, female, aged approximately 65, whose both son and daughter were physicians, was seized with two severe episodes of precordial distress while attending a local theater. She was transported by taxi to the hospital and was admitted in a most precarious state. Nausea, vomiting, dyspnoea, cyanosis, orthopnoea was most severe. Apprehension was severe. Electrocardiographic studies manifested a most severe grade of posterior and lateral wall infarction. Within twenty-four hours the arrhythmia of auricualr fibrillation ensued. Unnecessary and absurd therapeutic discussions were held at the bedside adding to the discomfort and apprehensive state of the patient. Unbeknowing to me, the physician's daughter had administered some tablets to minimize the nausea of her mother—the self same tablets which she was utilizing to thwart off her nausea associated with a pregnant state. Later the ingredients were demonstrated to the daughter physician and one of the ingredients was a cardiac stimulant. Quinidine sulphate, grains 24 in divided doses were administered daily; larger doses apparently were not well tolerated, however this thought must be tempered since at least six physician friends, including the son-in-law who is an X-ray specialist held frequent discussions within the hearing of the patient. The irregular ventricular response of approximately 130 per minute eventually was eliminated and a normal sinus rhythm prevailed, with an apical rate ranging between 70 and 80 per minute depending upon the time of day, etc. A most hectic course was experienced and therapy was employed as in other cases, however, substitution therapy for the aminophylline was instigated because one physician expressed the opinion that nausea perhaps developed and might be eliminated by the utilization of other xanthine derivatives; further, that rectal administration might be the procedure of choice. Recovery appeared apparent, yet during the third week of hospitalization there was a sudden rise in temperature, increase in the respiratory rate, accelerated heart rate whose rhythm was regular, nausea, apprehension, etc. A differential diagnosis between a massive pulmonary infarct and a massive pneumonic consolidation was offered with greater credence to the former, although, there was no pain within the chest wall and no bloody expectoration. Varied consultations were held. The patient expired approximately twenty-one days after the onset of the occlusive state. (Incidentally, I attempted to eliminate myself from the case during the 10th, 11th, and 12th days of the illness when all signs and symptoms indicated that the patient would recover, but to no avail, my mental turmoil notwithstanding.)

Case No. 21, male, aged 65, suffered his first coronary occlusive state and was confined to his home for the usual six week period. A daughter who is a nurse, together with the rest of the family, evidenced a splendid degree of intelligence. A nephew, who is a doctor, first informed me of his relationship some three weeks after the onset of the illness. A hospital bed was acquired, oxygen tank and further special nurses were obtained. The usual therapy was employed, including Dicumarol in 100 mg. doses the first week and thereafter 50 mg. doses. The patient was a smallish type of individual weighing approximately 110 pounds. The entire clinical course, with the exception of the first 10 days in which there were moderate recurrences of precordial pain about three to four A. M. and for which morphine and atropine were administered, was uneventful.

Case No. 22, male aged 62 years, suffered a spontaneous culmination of the intrinsic disease processes associated with sclerosis of his coronary vascular tree while working and filing reports. This was his first coronary insult. He was immediately hospitalized in a downtown hospital close to his place of employment. After two weeks in which the usual routine was employed and at a moment in which he was deemed free from possible hazards of further transportation, he was transported to a hospital in the Bronx and placed under the care of his own physician. The financial state of the family entered into the picture. The family physician continued my suggested routine and a splendid recovery ensued.

Case No. 23, male, aged 70 years, was afflicted with precordial pain and distress for two or three days and was then hospitalized by his physician. Electrocardiographic studies revealed fairly extensive anterior wall infarction together with moderate left bundle branch block. My suggested routine was employed by the physician particularly in reference to Dicumarol administration—and no hesitance was portrayed by the physician. An uneventful clinical course occurred.

Again in brief, because of the non-deleterious effect of dicumarol upon the myocardium and because of its easily controllable complication of hemorrhage, and because of the temerity in its possible usage away from laboratory advantage, and because of its conceivable prophylactic advantages, Dicumarol was originally utilized in 100 mg. doses in the first eight cases devoted to this study to vaguely ascertain its possible routine utilization in any instance of an acute coronary occlusive state; this routine was, as described above, modified twice and at this moment for the approximate 150 pound patient 100 mg. of Dicumarol are administered daily for the first week, then 75 mg. daily for the second and third week, and thereafter 50 mg. are administered for the remaining period of bed confinement.

In the twenty-three cases cited two mild hemorrhagic states occurred only during the period in which 100 mg. of Dicumarol were administered daily and these states occurred in one instance in the last two or three days of bed confinement and in the second instance several days following hospital discharge. Both hemorrhagic states were readily controlled, one spontaneously in which no therapy was employed and one in which vitamin K was utilized, as described. One death occurred which should not be included in the statistics of this study since we entered upon the therapeutic approach at a time when the patient was in a most critical state and practically moribund. The

second death readily is involved and thus, I choose to state that but one death occurred in my series of twenty-two cases, a percentage of 4.5 per cent. All other cases described herein returned to their usual physical and mental endeavors, and enjoyed essentially uneventful recoveries.

It is thus suggested that especially in areas where adequate laboratory facilities are unavailable, that the physician utilize the suggested approach described above in the administration of Dicumarol, and to modify the dosage as suggested and administered in the particular type of habitus as presented. It is again suggested that Dicumarol be utilized in all cases of the acute coronary occlusive state for its possible prophylactic advantage.

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Since the above paper was accepted for publication two additional cases have been successfully manipulated with the above regime, which decreases the mortality rate to four per cent

30 East 40th Street

THE BIOLOGIC CURE OF CHRONIC INFECTION

Howard B. Emerson, Jr., M. D.*
Tarentum, Pa.

Marriott (1), in 1927, stated that the eradication of sinus infections in children had been more effective in preventing recurrences of chorea, rheumatism or endocarditis than the removal of tonsils or adenoids. He further observed that it was not always possible to eradicate the infection. Marriott also found that nephrosis responded to treatment of associated sinus infection. He mentions also cases of encephalitis and idiopathic epilepsy which cleared up after treatment of infection of the paranasal sinuses.

Swift (2) and others, working with intravenous streptococcus vaccine in rheumatic fever, observed that most patients refractory to ordinary treatment had persistent signs of infection of the paranasal sinuses.

Cotton (3), in 1925, reported an increase in the rate of cure of psychotic patients from 38 per cent to 86 per cent by removal of foci of infection. Cotton also reported the cure of multiple sclerosis by this method of treatment. Moynihan (4) and William Hunter (5) reported spectacular results in nervous breakdowns, neurasthenias, depressions and psychoses by the treatment of focal infections.

Billings' (6) strong faith in the relationship of focal infection to systemic disease was well justified by the results he obtained in the treatment of arthritis and nephritis by the removal of foci of infection and treatment with vaccines.

The predominance of the paranasal sinuses as sites of infection (7) has cast doubt on the relationship of focal infection to systemic disease (8). For, even when treated by the best methods of otorhinolaryngological practice, biologic cure is difficult to attain and the relation between acute infections of the upper respiratory tract and reinfection is not fully appreciated (9). Furthermore, chronic sinusitis is often "silent" (10) and therefore untreated.

Swift (2) and his coworkers, in giving streptococcus hemolyticus vaccine intravenously to rheumatic fever patients, kept the dose very small in order to avoid confusion with the non-specific foreign protein effect. When tolerance developed to the vaccine renewed sensitivity developed during a rheumatic relapse or after an acute infection of the upper respiratory tract. They concluded from their studies that the favorable response of many patients to non-specific foreign protein therapy made evaluation of results difficult.

Meyer Solis-Cohen (11) thoroughly reviews the principles and methods of orthodox vaccine treatment. In general, vaccines are given in minute, increasing doses over a period of months or years. A focal or systemic reaction is considered a signal to reduce the dose of the vaccine.

Bivings (12) used autogenous and stock vaccines in the treatment of chronic infections of the upper respiratory tract in children with good results. He used high count vaccines when it became apparent that low count vaccines were not effective. He noted that a few children did not respond to treatment. Bivings recognized the problem as one of deficient immunity. Using autogenous vaccines with a count of four billion per c.c., he found it necessary to give only six to ten injections over a period measured in weeks. In using such potent vaccines the non-specific effect cannot be ignored.

Petersen (13) stated that the non-specific reaction, increases capillary permeability, produces a rise in the leukocyte count, antibodies, enzymes, thrombokinase and blood sugar. The leukopenia preceding leukocytosis is not paralleled by a

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transient fall in antibodies. The above changes, called the negative phase, are followed by a positive phase associated with decreased capillary permeability and increased resistance to toxins, among which are strychnine, phenol and protein split products. This increased resistance to toxins results in a state of desensitization. There is usually a slight lowering of blood pressure during the negative phase and occasionally gastro-intestinal hypermotility. Petersen stated also that colloidal metals and cincophen exert a non-specific and desensitizing effect. Petersen and Saelhof (14) noted a similar reaction to roentgen ray stimulation.

Foreign protein therapy has been given by means of milk injections intramuscularly but usually in the form of intravenously administered typhoid vaccine. Jobling and Petersen (15) refer to the use of typhoid vaccine subcutaneously by Fraenkel.

Miller (16) presented the results of foreign protein therapy in acute infections in 1921. Using a colon bacillus vaccine intravenously in typhoid fever, he found that in 20 per cent of cases the disease ended by crisis after from one to three injections. He used this form of therapy also in typhus fever, diphtheria, sepsis, pneumococcus pneumonia, influenzal pneumonia, syphilitic iritis, gumma, trachoma, corneal opacity with or without choroiditis and in bacterial endocarditis. Miller found no temporary or permanent benefit in bacterial endocarditis but refers to work by Kinsella who reported that the blood became sterile for 24 hours after the febrile reaction. In some patients with pneumococcus pneumonia or influenzal pneumonia crisis resulted after a single injection of foreign protein. In a series of cases with influenzal pneumonia the mortality in those given foreign protein therapy was 11.3 per cent, in a control group 31 per cent.

Miller and Lusk (17) in 1916 used intravenous foreign protein therapy in arthritis. They reported good results in 20 per cent of patients after from one to thirteen injections. They noted a strong tendency to recurrence which they believed was probably due to the persistence of a focal infection. They stated that the endocardial involvement was also controlled (18). They avoided injections when the heart power was poor. Cowie (19) used from one to ten injections of typhoid vaccine intravenously in arthritis and reported a complete cure in some cases. He reported relief from pain even when the focus of infection was not removed.

Culver (20) reported the use of typhoid vaccine intravenously in gonorrheal arthritis and epididymitis. He stated that if benefit was not noted after the second injection it was best to discontinue treatment. Culver used the same form of therapy in many skin diseases and reported temporary cures in chronic eczema and psoriasis.

Comroe (21) advises against the use of foreign protein therapy in rheumatic fever but states that in occasional obstinate cases attacks have been stopped by its use. He states further, in discussing foreign protein therapy in general, that if there is no improvement after four injections treatment should be discontinued.

From the foregoing paragraphs it is apparent that chronic infection has been incriminated as the etiologic factor in a number of serious diseases and that foreign protein therapy has found a wide application in the treatment of many conditions due to infection whether acute or chronic. The use of typhoid vaccine intravenously has never been very popular for obvious reasons. On the other hand many foreign proteins on the market prepared for subcutaneous use have failed because of their impotence and because of a tendency to use them in the manner in which orthodox vaccine therapy is given. The stock "cold" vaccines are potent. They have the advantage in that they rarely cause sensitization phenomena (22).

Method of Treatment

In the study reported below, 114 patients with chronic infections of the upper respiratory tract were treated by a series of injections of foreign protein administered subcutaneously. A stock "cold" vaccine (Immunovac*) was used, consisting of bacteria and soluble antigen of organisms commonly found in the upper respiratory tract equivalent to 2500 million organisms per c.c. An initial dose of 0.4 c.c. was given. This was increased by 0.1 c.c. with each succeeding injection. An increment of 0.2 c.c. was not found to appreciably affect the results but reactions were more shocking. Injections were usually given three or four days apart. From five to fifteen injections were required in most cases to eradicate the infection. In children, three or four injections beginning with 0.2 c.c. and increasing by 0.1 c.c. with each dose, were usually sufficient. After the onset of puberty, patients were treated as adults.

About 30 per cent of patients developed "colds" during treatment. Later in the study, it was found that the intramuscular injections of a therapeutic dose of bismuth along with the foreign protein injection resulted in disappearance of all symptoms of the "cold" within two days. The injection of bismuth was usually given within three or four days of the onset of the "cold." The treatment failed when the foreign protein reaction was poor, and occasionally when a good foreign reaction was obtained. Bismuth given orally in the form of Bistrimate** (23) tablets were also found to be effective. Twelve tablets were given, to be taken at the rate of two, three times daily. In children one-half to one-quarter this amount was given depending on the age. Since this combined treatment has been used, patients with potentially serious disease or very annoying symptoms associated with infection, have been advised to report on the first day of a "cold" after treatment was completed. Otherwise, they were advised to report if any "cold" lasted more than two weeks, at which time foreign protein injections were resumed and continued to the proper end point. The dose used was somewhat lower than the maximum dose reached previously depending on the time elapsed after the original series of injections. In individuals who

*Parke Davis & Co.
**Carroll Dunham Smith Pharmacal Co.

were retreated, it was found that tolerance was completely lost in most cases within three months.

Pertussis Topagen*, a vaccine prepared commercially for intranasal use in whooping cough was found to deliver an appreciable systemic shock in the presence of non-specific infection. (Conversely, the stock "cold" vaccine used as described above has been found effective in several cases of whooping cough.) Its use has not been found to accelerate cure of the chronic infection.

Patients with allergic rhinitis or asthma or both, whether seasonal or non-seasonal did not require any treatment other than the foreign protein injections. If treatment was completed before the pollen season had passed, those sensitive to pollens were advised to use increasing doses of "Pertussis Topagen" intranasally beginning with three drops in each nostril. The effect lasted about one week after each administration. Patients with asthma and negative skin tests did not require any further treatment when the chronic infection of the respiratory tract was eradicated.

The stock "cold" vaccine used is also prepared for oral use. It has been found to be effective in a few cases in children but because of its unreliability is no longer used. The initial dose was two tablets, increasing by two tablets each day for four doses. The tablets were given all at once before breakfast.

Iodides (24) have been used during the treatment in some cases but without any appreciable effect on the results. They have, therefore been avoided because of the frequent occurrence of iodism.

Effects of Treatment

The expected reactions to treatment were not severe as evidenced by the fact that rarely did a patient lose a day's work during treatment. Malaise lasted for from one to two days. Temperature rise was slight. A chill was felt to be due to the accidental introduction of vaccine into the blood stream. During a course of treatment, a "peak" systemic reaction was reached after which subsequent higher doses produced less reaction, both locally and systemically. Following the "peak" reaction, the local and systemic symptoms originally complained of usually improved considerably or disappeared. The higher doses occasionally produced weakness, drowsiness and anorexia. "Heartburn" and abdominal cramps occurred occasionally. There were no serious untoward reactions. Mild confusion following an injection was a rare reaction. This occurred in non-alcoholic as well as alcoholic patients. When urticaria occurred, it was found to be associated with a food allergy in most cases but whether the allergenic food was removed from the diet or not the urticaria gradually improved with subsequent injections. Mild epistaxis and gingival hemorrhage occurred rarely. In patients with mild or latent asthma, transient mild exacerbation occurred after the first few injections. In severe asthma this was not apparent but rapid improvement took place.

The focal reaction usually began with the first injection but occasionally did not occur until the seventh, or other injection. It usually continued with subsequent injections but occasionally subsided to occur again after a variable number of injections. The reaction began within a few hours after injection or was sometimes delayed as long as three or four days, in which case it was more or less violent. The focal reaction consisted in an increase in the discharge from the nose, usually post-nasal, at first yellow, later cloudy and finally clear. Headache often preceded the discharge. The pharynx occasionally became acutely inflamed and painful, simulating an acute exogenous infection. Penicillin has been used in some cases with a severe focal reaction but has not been felt to hasten subsidence of the reaction. In some cases, increase in the post-nasal discharge did not occur but congestion in the turbinates and evidence of chronic infection in the throat disappeared.

The action of Bismuth given in the manner as described above when a "cold" developed was more apparent when given by injection. Within a few hours a profuse post-nasal flow of thin, viscous mucous began, associated with increased nasal congestion. The reaction subsided overnight and all symptoms of the "cold" disappeared within two days. The focal reaction to subsequent injections of foreign protein continued, however, as long as the original bacterial infection had not been eradicated.

Criteria of Cure

The indicator of the end point of treatment was the upper respiratory tract and, if present, the systemic disease. When proper response in the systemic disease was obtained, the nose and throat appeared healthy and there was no perceptible post-nasal drip, the patient was considered to have a presumptive cure. If symptoms or signs of the original infection did not recur following a "cold" or if symptoms or signs were not present when the patient was seen five months or more after treatment, the patient was considered to have obtained a biologic cure of the infection. With the use of bismuth and foreign protein as described, many patients were not subjected to a "cold" of natural duration as a test of cure. If recurrence of symptoms took place following a "cold" five months or more after treatment, this was considered a reinfection.

Contraindications to Treatment

Barr (25) lists as contraindications to foreign protein therapy: serious cardiac or renal disease, marked hypertension and marked debility. Clendening (26) mentions quiescent tuberculosis, diabetes and pregnancy as contraindications. None of these conditions has been found to contraindicate the use of foreign protein therapy given by the method described. "Serious cardiac disease" and "marked debility" must be qualified as will be shown later. The treatment has been used in one case of tuberculous bronchopneumonia (not here reported) along with streptomycin and penicillin with good result. The presence of tuberculosis should be recognized, however, and proper precautions taken. With thoracic surgery becoming

*Sharp and Dohme.

more popular, the use of foreign protein (tuberculin) in tuberculosis as used by Koch and Sonnenberg (27) may again become pertinent, although the use of the "specific" protein is no doubt unwise.

Diagnosis of Chronic Infection of the Upper Respiratory Tract

Wachsberger (28) has pointed out that the chronic sinusitis of adults usually begins in child hood. The infection must therefore, be considered as a lifetime disease with varying manifestations governed by the age period, hereditary predisposition of the individual, and the infecting organism. Under hereditary predisposition probably should come "capillary pattern" (29) and the tendency to develop specific vitamin or other deficiencies leading to specific disease entities.

In "silent" infection, the focal reaction following administration of foreign protein therapy serves to demonstrate the presence of infection.

Transillumination of the sinuses often assists in the diagnosis but is less important than the history and direct examination of the nose and throat. Transillumination has proved invaluable in the location of a non-draining sinus in one patient with rheumatic fever in whom antrotomy was necessary.

Nasal cultures and roentgenograms of the sinuses have not been necessary.

Analysis of Cases

Of 114 patients treated in the series reported, 63 were male, 51 female. The oldest was 81, the youngest, eight months. Thirty-nine had had tonsillectomy. Six had had a submucous resection of the nasal septum, two had had antrotomy previously. Twenty-six or 22.7 per cent gave a history of allergic manifestations or had allergic symptoms when seen. As mentioned previously, 34 or 29.8 per cent developed "colds" during treatment. Of 33 trials of the combination of bismuth and foreign protein in the treatment of the "cold," the result was successful in 21 or 63.6 per cent. A presumptive cure was obtained in every child and in 75 or 77.3 per cent of all adult patients treated.

The average number of injections given was 9.5 in adults, four in children. The greatest number of injections given to a patient was 28, the maximum dose of "vaccine" was 4.6 cc.

Of the 114 patients, 17 were children under puberty. Twelve adults and one child were lost in the follow-up period. Treatment in one adult was incomplete because of removal to a different section of the country. Results in the remaining 84 adults and 16 children are given in Table I.

In several cases, the infection recurred without intervening acute infection of the upper respiratory tract as late as four and one-half months after treatment was completed so that cases followed between four and five months were classed as questionable cures. Recurrence usually took place within one or two months after treatment, however. All patients but a few as noted in the accompanying table were seen personally at the end of the follow-up period. The number of biologic cures listed in the table represents the rate of cure for patients treated in the Allegheny Valley during the winter and spring months of the year 1947–48 (a severe winter). It was felt that recurrence was not likely for many who, checked in mid-October, had passed through what was considered to be a critical period—the summer months. The three recurrences in children followed acute infections of the upper respiratory tract and were probably reinfections, but because of the short period of follow-up, it could not be certain that a biologic cure was obtained. The same was true for some of the recurrences in adults.

Some adults dated the onset of their symptoms in the upper respiratory tract to childhood, most stated that the symptoms had been present for "years." Often the history of chronic bronchitis, rheumatic fever, etc., in childhood placed the onset of the infection at a much earlier date than that given by the patient.

All patients were benefited by treatment, whether or not recurrence took place. The symptoms after recurrence, both local and systemic, were in general less severe and often some symptoms complained of originally did not return. Of the 20 patients of all those treated in whom a presumptive cure was not obtained, only one was considered to be a "hyporeactor." This patient, a 40-year-old female experienced only two good reactions in 21 injections. The first focal reaction occurred at the seventh injection, the other at the 21st. The maximum dose of "vaccine" given her was 4.4 cc. Pain and swelling in the left ankle complained of when first seen, however, disappeared during treatment and had not returned two and one-half

TABLE I

Results of Treatment in 84 Adults and 16 Children

	BIOLOGIC CURES (Follow-up 5–11 mo.)		QUESTIONABLE CURES (Follow-up 4–5 mo.)		RECURRENCES		REINFECTION	NO PRESUMPTIVE CURE	
	NO.	%	NO.	%	NO.	%	NO.	NO.	%
Adult..	29	34.5	11*	13.1	27	32.1	2	17	20.2
Children	11	68.7	2**	12.5	2	18.7	?		

*Two contacted by telephone followed 4½ and 6 months respectively.
**Followed 6 months or more via information from parent. Questionable because not seen personally.

TABLE II

"ENTITIES" ENCOUNTERED IN ADULTS TREATED FOR CHRONIC INFECTION OF THE UPPER RESPIRATORY TRACT

1. Arteriosclerotic Heart Disease	2	11. "Male Climacteric"	5
2. Rheumatoid Arthritis	10	12. Multiple Sclerosis	1
3. Bronchial Asthma	4	13. Optic Neuritis	1
4. Chronic Hepatitis	1	14. Peptic Ulcer	1
5. Cirrhosis	1	15. Psoriasis	2
6. Cystitis, Pyelitis	3	16. Psychoneurosis	7
7. Diabetes Mellitus	3	17. Retinal Hemorrhage	2
8. Histamine Headache	1	18. Tic Doloreux	1
9. Essential Hypertension	1	19. "Salt Wasting" Nephritis	2
10. Hyperthyroidism	1		

"ENTITIES" ENCOUNTERED IN CHILDREN TREATED FOR CHRONIC INFECTION OF THE UPPER RESPIRATORY TRACT

1. Chronic Rheumatic Fever	2	5. Chronic Bronchitis	1
2. Acute Rheumatic Fever	2	6. "Feeding" Problem	1
3. Non-Rheumatic Growing Pains	1	7. Behavior Problem	1
4. Pyelitis	1		

months later. Of the other patients, several were discharged with a "cold," several were discharged before the proper end-point, as shown by later experience, had been reached. Of the remainder, some were discharged because of poor cooperation on the part of the patient in the matter of imbibition of alcohol. (The avoidance of alcohol was considered as important as in specific urethritis.) Others discharged themselves when improved or were given a rest because of prolonged treatment. In some, the reactions, although good, always fell short of presumptive cure. These patients were advised to resume treatment later. Most patients were skeptical of the treatment but skepticism was felt to have interfered with pursuit of treatment only once. The reactions to injections were naturally a factor in the decision to interrupt treatment when this was prolonged.

Few of the patients seen sought medical attention for "sinus trouble." Although many had recognized its presence for years they did not usually relate mental and physical symptoms complained of, to the infection.

Fatigue and nervous tension were noted by the majority of patients. Habit tics were noted in a few patients. Precordial pain was frequently noted and was a major complaint in a few cases. The ulcer symptoms complex without demonstrable ulcer was present in three patients. Mental reactions of one type or another were almost universal in children as well as adults. Euphoria, depression, confused states, loss of memory, poor power of concentration and weeping without provocation in both males and females were noted. The "shallow affect" was common. A common complaint of many patients was that the arms and feet "went to sleep" easily. In some patients, the face was flushed when first seen but in most, the facial color was uniformly pale. All of these reactions were demonstrably due to the chronic infection. Anemia was rarely encountered in this series and was never severe enough to cause symptoms. Most patients had low normal blood pressures. Although in these the blood pressure did not change appreciably with treatment, an increase in the force of the pulse was readily apparent in some individuals and symptoms that might have been ascribed to low blood pressure disappeared.

The "entities" encountered are listed below. Several conditions may have been present in one individual.

Of the two cases of arteriosclerotic heart disease one, a woman aged 72 complained of fatigue, palpitation and a feeling of substernal fullness. These symptoms disappeared with treatment and had not recurred six months later although premature beats were still frequent. The other, a man aged 58 was hospitalized with decompensated heart disease and auricular fibrillation. After digitalization and several injections of a mercurial diuretic, foreign protein therapy was begun and continued for seven injections over a period of two months when the patient was lost. This man returned to work and symptoms of decompensation did not return during this period.

Of the three cases of asthma, two were mild, the other had severe attacks. None of these cases is reported here in detail. It will merely be emphasized here that treatment must be carried to the proper end-point when infection is responsible, and the "initial" dose should not be less than 0.4 cc.

Of the ten cases of rheumatoid arthritis, all were mild except the case reported below. In one case recurrence of pain in the finger joints and knees recurred four and one-half months after treatment simultaneously with recurrence of postnasal drip. Arthritic symptoms disappeared in every case when the focal infection was eradicated. Aggravation of the arthritis during treatment was not incapacitating except in the case reported below. This case also had gout. One other case with gout (uric acid level 5.15 mg. per cent) had no arthritic symptoms but only variable hyperemia and pain over the metatarsophalangeal joints. Treatment of the focal infection resulted in slow disappearance of these symptoms. They had not recurred six months later, despite the presence of a "cold."

One case of liver disease is reported below. The case of cirrhosis also had a low blood chloride and marked thirst, asthenia and low blood pressure of the type reported by Thorn (30) and Kugel (31).

A biologic cure of the chronic infection of the upper respiratory tract was obtained in this patient. Several blood chloride determinations before and after treatment showed that the chloride level rose spontaneously to a normal level with eradication of the infection. The blood phosphorus, which had been elevated before treatment also returned to a normal level after treatment. This patient developed mild, generalized edema and increased tendency to ascites after treatment which subsided, but a strong tendency to increase in the edema persists. One other patient, a man aged 33, had a similar association of symptoms with low blood chloride. He was well 11 months after treatment and had had no edema during several acute upper respiratory infections as occurred in the case with cirrhosis. The blood chloride determination was not repeated after treatment.

The relation between cystitis and pyelitis and focal infection has been emphasized by Crawford (32).

Of the three cases with diabetes, one is reported below because he also had angina pectoris. The insulin requirement was not felt to be raised during or after treatment in these patients but in one case not reported in this series, this was felt to be the case. Two of the cases were seen first by ophthalmologists because of visual disturbances due to retinal "hemorrhages."

One case had histamine headache and had been successfully desensitized with histamine previously by the author. The headache recurred one year later following a "cold." The response to foreign protein therapy was good. Headaches had not recurred four and one-half months after treatment.

One case of essential hypertension is reported below. This patient also had arthritis. The frequent association of these two diseases has been noted by Walker (33).

The one case of hyperthyroidism, a woman aged 54, was well ten months after treatment. She had taken no iodine for three months when last seen. The aggravation of Grave's disease by acute and chronic infection has been noted by Squier (34).

The case of multiple sclerosis is reported below.

Five cases were diagnosed as male climacteric. Four were markedly improved after administration of testosterone. Only one requires testosterone since the chronic infection has been treated. One was treated for the chronic infection first and testosterone given later because of difficulty in obtaining a presumptive cure. This patient has been well for the past three months with no medication.

The patient with optic neuritis was almost blind in the right eye because of traumatic cataract. The vision in the left eye was essentially normal after eradication of the chronic infection.

One case had had a duodenal ulcer for 20 years. The usual antacid and sedative therapy was given during and after foreign protein therapy so that the effect of treatment of the infection could not be properly evaluated.

The two cases with psoriasis were improved but not cured, although recurrence of infection occurred in both of these individuals.

The use of foreign protein therapy in tic doloreux is not new (35). The patient with this condition also had a severe infectious eczematoid dermatitis of the entire right leg below the knee. Neither of these conditions had recurred four months after treatment of the patient's focal infection.

In seven cases, a diagnosis of psychoneurosis was made—not because of many bizarre and widespread physical symptoms which were obviously due to focal infection but because of the exaggerated mental reaction to the symptoms. These patients were not cured of their hypochondriacal tendency but with the removal of physical symptoms and brightening of the mental faculties, they required little or no medical attention. In one patient, the psychoneurosis approached psychotic proportions. This case is reported below.

All but one of the cases of rheumatic fever had heart murmurs—in one mitral regurgitation was present—in two mitral stenosis and regurgitation were present. All had had joint pains in the past or when seen. Treatment of three cases was uneventful. In each, biologic cure of the infection was obtained. All have had acute upper respiratory infections since treated without recurrence of rheumatic symptoms. The follow-up period has been from six to 11 months. The fourth case is reported below.

In one patient, a diagnosis of non-rheumatic growing pains (36) was made. Aching in the legs complained of by this five-year-old girl was a common symptom in adults as well as children and was demonstrably due to chronic infection.

The child with chronic bronchitis was aged seven and had had the condition since infancy. This patient was the "behavior problem" listed also. She was irritable, whined and cried frequently and was unmanageable at home and at school where she did poorly. After eradication of the infection in the respiratory tract, the patient became quite tractable and did well in school. Five months after treatment reinfection occurred following a severe "cold." The "behavior problem" returned but the bronchitis did not. A good result was again obtained following retreatment.

The "feeding" problem listed was the youngest patient seen—eight months. She had frequent "colds" with diarrhea and each time seen, one ear drum membrane or the other was found to be reddened. The child ate poorly and at eight months weighed 17 pounds (weight at birth, 9½ pounds). The cry was weak. Following foreign protein therapy, she ate well and gained weight rapidly. Diarrhea did not occur with subsequent "colds." The child became vigorous, the cry strong. Marriott (1) emphasized the fact that in marasmic infants or in infants who were "feeding problems," chronic infection of the middle ear and antrum was often responsible. The following illustrative cases are presented:

Essential Hypertension

Case 104—A 64-year-old white female complaining of nervousness, occipital and frontal headaches, nasal obstruction and pain in the right shoulder and finger joints for about four years. She had also noted dyspnea and palpitation on climbing one flight of stairs for about four years. The patient stated that her blood pressure had been high for at least four years. One brother and the grandmother had died of a stroke. One sister had hypertension.

Physical examination revealed an elderly female weighing 166 pounds, 61½ inches in height. The speech was rapid and slurred. The retinal arteries were constricted. The nasal mucosa was congested and dry. The pharynx was red. Upper and lower dentures were present. There was a soft systolic murmur in the aortic area. The heart was moderately enlarged to the left. Blood pressure was 220/100.

Foreign protein therapy subcutaneously as described was given. After the fourth injection, the patient noted a postnasal discharge. Blood pressure at this time was 190/90. After the fifth injection, the blood pressure was 190/90, after the sixth, 185/80, after the seventh, 145/70. The nose and throat appeared healthy at this time but the patient noted a slight postnasal discharge. One week later the patient had a "cold"—blood pressure at this time was 140/80. There was no evidence of recurrence of the old infection. Twelve "Bistrimate" tablets were prescribed and an injection of foreign protein given. One month later the nose and throat appeared healthy but the patient complained of right temporal and occipital headache. She stated the "cold" had lasted one week. The blood pressure was 170/80. The right ear was negative to examination but the patient was observed and three weeks later a purulent otitis media developed. Foreign protein injections were resumed. Three hundred thousand units of penicillin in wax were given with the first injection. During this period, the patient noted a postnasal discharge from the right side and slight sore throat. The diastolic pressure never rose above 80 mm. of mercury during this period although the systolic pressure continued around 170 mm. After eight injections, all symptoms had disappeared and the blood pressure was 140/80. When seen two months later, the patient had a mild "cold." There was no evidence of recurrence of the old infection. She had had no headache or joint pains or upper respiratory tract symptoms in the interval. She had been less nervous and had not been dyspneic on exertion. The blood pressure was 145/75. The patient was observed and two weeks later nasal congestion and postnasal discharge were still present. The blood pressure was 190/90. Foreign protein therapy was resumed.

Rheumatic Fever

Case 96—A 14-year-old white female, first seen March 3, 1948, complaining of pain in the soles of the feet, both arches and calves, of one and one-half years' duration. The pains had been worse for five days. The patient had had a sore throat two weeks previously and had noted an increased nasal discharge since. The patient had had running ears for one month at the age of two. Following a sore throat one year previously, she had been in bed three weeks with rheumatic fever.

Physical examination revealed a well developed, well nourished adolescent female weighing 113 pounds and 61 inches in height. The temperature was 97.6, pulse was 88 and blood pressure 100/60. The nasal mucosa was congested and red. The right maxillary sinus was dark to transillumination. A short systolic murmur was present in the mitral area. The second metatarsophalangeal joint of the left foot was painful on pressure. The sedimentation rate was 23 mm. in one hour.

The patient was given 0.3 cc. of "Immunovac" subcutaneously. The following day the pains in the foot had disappeared. An increased postnasal discharge was noted by the patient. Following the third injection, pain and swelling developed in the left knee. This subsided in a few days and following the fourth injection pain and swelling developed in the right knee and foot. Following subsequent injections, pain and swelling occurred in one joint or another of the lower extremities but were less severe. The joint reaction was also produced by an injection of triple typhoid vaccine. During the treatment, the patient felt progressively better. Mild joint pains continued, however. The temperature did not exceed 100.2 (following the first injection) and the pulse did not exceed 108 when seen (three or four days after each injection). Five weeks after she was first seen a right antrotomy was performed because of continued failure of the right antrum to transilluminate. This was followed several hours later by a profuse, yellow discharge from the right nostril and rapid disappearance of all joint pains. Nine more foreign protein injections were given without joint reactions (maximum dose 2.4 cc.). At this time the postnasal drip was clear but the nasal mucosa on the right side was still red. Treatment was interrupted at this point. When seen three months later, the patient looked well and stated she had felt well during the summer but had had a slight postnasal drip. She had gained four pounds. She had had a "cold" for one week. The nasal mucosa on the right and the pharynx were red. After the administration of a mixture of bismuth and "Pertussis Topagen," foreign protein injections were resumed, beginning with 0.4 cc. of "Immunovac." After eight injections, a presumptive cure was obtained. No joint reaction occurred during these injections.

Diabetes, Angina Pectoris

Case 101—A 43-year-old white male first seen on May 28, 1948, complaining of chronic fatigue and dyspnea on exertion for more than five years. He had lost about 45 pounds during this period. He had noted blurring of vision at times for one and one-half years. For two months he had experienced a sharp pain across the upper sternum on exertion requiring sudden cessation of activity. This occurred on walking two blocks or on pushing a lawn mover about 50 feet. He had noted slight swelling of the ankles occasionally when working. He had had frequent headaches for about 10 years.

He had been treated for "sinus trouble" with nasal packs ten years before and again one year before. He noted that his arms and legs had "gone to sleep" frequently for years. On routine examination for glasses two months before, retinal "hemorrhages" had been noted and the patient was advised to have a blood sugar determination. This was 260 mg. per hundred cc. He was placed on a low carbohydrate diet but because of unsatisfactory level of the blood sugar, was hospitalized for control of the diabetes with insulin. He was discharged taking 20 units of protamine-zinc insulin daily on a diet of 1600 calories consisting of: carbohydrate—100 Gm., protein—120 Gm., fat—80 Gm. When first seen his fasting blood sugar was 145 mg. The patient felt better but still complained of the symptoms listed above. He stated also that sexual potency had been diminished for three years. He still had noted blurring of vision, especially on close work.

Physical examination revealed a pale, tired looking male 70¼ inches in height, weighing 180 pounds. The temperature was 98 degrees, pulse 84 and blood pressure 95/60. Retinal examination showed perimacular petechial hemorrhages. The nasal mucosa was boggy, the anterior pillars of the fauces were red. Both maxillary sinuses were dark to transillumination. General examinations was otherwise negative, neurological examination disclosed diminished patellar and absent achilles reflexes. Foreign therapy, beginning with 0.4 cc. of "Immunovac" was begun. A good focal reaction was obtained. After the third injection, there was no exertional chest pain. Dyspnea and fatigue gradually disappeared and sexual potency improved. Headache did not recur and none of these symptoms have recurred five months after treatment. A presumptive cure was obtained after eight injections. The patient was advised to eat more when first seen but to avoid concentrated sweets and keep the daily quantity of food fairly constant. Two weeks later the blood sugar was 161 mg. During the summer the blood sugar ranged from 122 to 150 mg. Insulin was stopped on July 22, 1948. The blood sugar three weeks later was 150 mg. per cent. Urine specimens examined in the morning and at 4:00 P. M. had all been sugar free during this period. The patient noted little difficulty in focusing his eyes during and since treatment. On November 5th the blood sugar was 172 mg. per cent. The patient had been seen by an ophthalmologist in August. No recent retinal pathology was noted. The improvement noted was sustained. The weight had dropped from 180 to 175 pounds during the month after completion of foreign protein therapy but has remained at this level since. The blood pressure has not been above 110/60 since first seen. On November 8th, the patient reported because of a "cold" of one day's duration. An injection of bismuth was given intramuscularly and 0.4 cc. of "Immunovac" subcutaneously. The "cold" disappeared in a few days. When seen one month later the blood sugar was 122 mg. The patient felt well and had noted no visual disturbance but petechial "hemorrhages" were noted in both retinae. The nose and throat appeared healthy and no nasal discharge was noted by the patient. One month later, the fundi showed only several "petechiae" (no new scars) above the left optic disc. There was no evidence of recurrence of nasopharyngeal infection.

Chronic Hepatitis

Case 82—A 53-year-old white male first seen on February 28, 1948. He was brought into the office by his wife because of spells of transient confusion and forgetfulness of several weeks' duration. The wife stated he sometimes left his overcoat at work even in cold weather, sometimes took the wrong bus after work and did not return home for hours. He had had a "cold," cough and sore throat for two weeks and weakness had been marked during this period. The patient had had frequent, loose stools since the onset of the "cold." He had had frequent "colds" with severe cough for the past two years. One year before he had had "rheumatism" in the left shoulder. He stated that he had had "rheumatism" as a child. He had noted a "rolling" in the abdomen on lying down at night for about five years. He had been unable to sleep more than a few hours at night for years. He stated he had always drunk "gallons" of water a day and perspired a great deal. Sixteen years previously he had had a "nervous breakdown" lasting about four months. The patient had drunk considerable alcohol daily when single. He had been married for 16 years and during this time drank beer frequently but not excessively. The appetite had been good. He had lost no weight. He had been examined at a well known diagnostic clinic in October, 1941, where he had gone because of low back pain and gaseous distention. He was considered to have had an irritable colon at that time. In September, 1946, he returned to the clinic because of a recurrence of the same symptoms of two years' duration. A few diverticula of the colon were found by x-ray examination at that time. The only other significant finding was a 16 per cent retention of bromsulfalein at the end of 30 minutes. The icterus index was normal. The stools were negative for occult blood. He was believed to have a chronic hepatitis and was placed on a reducing diet, choline and vitamin B-complex by mouth and crude liver injections. Four months later bromsulfalein liver function test showed eight per cent retention of dye. He was instructed to continue taking B-complex capsules and choline. Two months later he returned with an acute infection of the upper respiratory tract. The bromsulfalein liver function test at this time showed 40 per cent retention of dye at the end of 30 minutes. The physician in charge questioned the reliability of this finding. In July, 1947, three months later, he was feeling well and the bromsulfalein liver function test showed 12 per cent retention of dye. He was placed on a high carbohydrate, high protein, low fat diet and instructed to continue B-complex capsules and choline. In October, 1947, he felt well. He had gained 25 pounds in the past year. Bromsulfalein liver function test showed 14 per cent retention of dye. Chloride and phosphorous

determinations were not made during the visits to the clinic.

Physical examination revealed an obese, nervous male with a staring expression. The speech was rapid and slurred. The memory for recent and remote events was poor. The temperature was 99 degrees, pulse, 80; blood pressure, 140/65; weight, 198 pounds; and height, 66¾ inches. The right maxillary sinus was dark to transillumination. The nasal and pharyngeal mucosa were red. General, and neurological examinations were otherwise negative except for a coarse tremor of the hands and a 2+ enlargement of the prostate gland. Urinalysis was negative (specific gravity 1.017). The other pertinent laboratory findings were: N. P. N. 40 mg.; blood chloride, 610 mg.; calcium, 15.9 mg.; phosphorus, 15.0 mg.

Foreign protein therapy was begun at the first visit. After the second injection, the patient came to the office unaccompanied by his wife. His mental condition and physical energy improved rapidly. The mild diarrhea cleared up. "Rolling" in the abdomen became less severe.

After the third injection, he was able to sleep for six hours at night and did not wake up terrified at night as he had formerly. The tremor of the hands disappeared. Good focal reactions had been obtained during the treatment and the postnasal drip had diminished and become clear. Two days after the fourteenth injection (two months after the beginning of treatment) the patient developed a severe sore throat, fever and prostration. This reaction was associated with a thick, yellow nasal discharge. The right maxillary sinus transilluminated at this time, but poorly. After two more injections, the nose and throat appeared healthy and there was no perceptible postnasal drip. One month later the patient felt well but had a slight cough. There was slight pharyngeal redness at this time. The patient was placed on methyl testosterone therapy (10 mg. t.i.d.) in an attempt to increase resistance before resuming foreign protein injections. The nose and throat appeared healthy when seen two weeks later but slight cough continued. A foreign protein injection was given at this time and he was advised to return in one month. He returned three months later complaining of fatigue and palpitation for several weeks. He had taken no testosterone for two weeks because of the belief that it was responsible for the palpitation. Auricular fibrillation was present with an apical rate of 140. He was digitalized with good result. A few days before this visit the blood chloride was normal, serum phosphorus was 2.3 mg.; calcium, 12.1 and bromsulfalein test showed no retention of dye after 30 minutes. There was slight redness of the lateral walls of the pharynx at this visit. The right maxillary sinus transilluminated, but poorly, as before. Foreign protein injections were resumed and were continued every seven to 14 days. A presumptive cure was again obtained after 10 injections. Normal sinus rhythm had been re-established at this time. During the time this patient was seen, he continued taking vitamin B-complex capsules orally and he continued to adhere to the high carbohydrate, high protein, low fat diet. The patient felt more vigorous after the beginning of treatment and continued working throughout the period seen except for a few days after the severe focal reaction noted above.

Psychoneurosis

Case 70—A 24-year-old nurse who had been married four months previously. She had quit her job as a dispensary nurse three months previously because of a feeling she was not getting a "square deal." She stated that she had always been "unhappy," that she had been chronically depressed, anxious, and tense since childhood. She also stated that she had had frequent feelings of unreality since childhood. As a nurse in the Navy, two years before, she had begun a psychoanalysis but had broken off seeing the psychiatrist because she felt she "wasn't getting anywhere." In 1947, after discharge from the Navy, she was hospitalized for one week when she underwent a "narcosynthesis." At this time her father was told that she was "unhappy" because she had not wanted to be a nurse. One month before first seen she had begun a series of eight electric shock treatments as an out-patient on the advice of a psychiatrist. She felt worse during this period and did not return for the eighth treatment. The patient had had frequent "colds" since childhood. The tonsils had been removed at five years. She had had a bronchitis during one summer at eight years. She had had measles at five years, scarlet fever at 10. She had been treated for sinusitis with sulfadrugs and nasal packs in 1942. For three days before seen she had noted purulent nasal discharge.

The family history was significant in that one brother had night terrors and frequent feelings of unreality.

Examination revealed a well developed, white female, 64 inches in height, weighing 135 pounds. The pulse was 80 and blood pressure 90/45. The patient presented an unkempt appearance. The expression was staring. There was obvious mental retardation but the emotional reactions were not appreciably affected. The skin color was poor. The nasal mucosa was red, there was purulent material under the right middle turbinate. Islands of lymphoid tissue in the pharynx were red. Neurological examination was negative.

Foreign protein therapy was begun. After the fifth injection, the patient began to complain of nausea during the day and occasional vomiting in the evening. She had not menstruated two weeks before as expected. A Friedman test was positive. Treatment was continued. At the sixth injection the patient was also given a therapeutic dose of bismuth intramuscularly because of a "cold" of three days' duration with good result. At the time of the eighth and last injection, the nose and throat appeared healthy and no postnasal drip was noted. During the treatment there was a progressive brightening of the patient's countenance and a return of color in the cheeks. The general appearance became neat. The mental retardation disappeared. The patient talked more freely and

blamed her mother for her unhappiness. When seen two weeks later she was bright, happy and energetic. The marked change was apparent to her husband. When seen five months later, she had returned to the state she was in when first seen. She had had two "colds" since seen, the first four months after treatment. This was associated with a bronchitis. Postnasal drip, nasal stuffiness and slight cough had continued since. The patient had been advised by her obstetrician to see a psychiatrist.

"Gouty" Arthritis

Case 14—A 51-year-old white male first seen on February 14, 1948, because of an acute infection of the upper respiratory tract of two days' duration. The patient stated he had a "cold" and cough continually during the winter time. He also stated that he had had arthritis every winter for the past six years. The year before he had been off work two months because of this. Three weeks before seen he had had three intravenous injections for mild joint symptoms in the right elbow and left foot proximal to the big toe.

Examination revealed a well developed individual, 65 inches in height and weighting 184 pounds. Temperature was 100.4 degrees, pulse 108 and blood pressure 120/65. The nasal mucosa was congested and red. The pharynx was also red. The maxillary sinuses were dark to transillumination. There were no signs of arthritis at this time. Blood uric acid was 6.65 mg. per cent. Foreign protein therapy subcutaneously was begun. Following the second injection, the patient developed severe pain, redness and swelling in the right elbow, left ankle and over the dorsum of the left metatarsophalangeal joint necessitating confinement to bed. The next two injections were given at the patient's home but after this he was able to come to the office although still having pain and swelling in the joints noted. Tincture of colchicum, given to the point of producing loose stools did not affect the joint symptoms. A presumptive cure was obtained after 18 injections, given over a period of two months. The patient had no joint symptoms at this time. He returned ten days later with mild pain in the left ankle and left metatarsophalangeal joint. He had a number of devitalized teeth which had not been examined by a dentist as advised when first seen. He was therefore advised to return after dental care, if symptoms persisted. When seen seven months later, the nose and throat showed no signs of chronic infection although the patient had a mild "cold." He stated he had had a "cold" several months before from which he recovered without any residual postnasal drip or other local symptoms. He had no joint symptoms in the interval. X-ray examination of the teeth had disclosed no abscesses so that none had been extracted.

Multiple Sclerosis

Case 72—A 39-year-old white male first seen on April 2, 1948. He stated that five years before he had first noted weakening of the arches, followed a short time later by diplopia and intention tremor. He had noted a weakness of the left arm for four years. The speech had become thick and slurred and difficulty in walking had been noted three years before. All the teeth had been pulled at the onset of the disease. Three years before he had been given 50 injections of histamine intravenously and from this time on the symptoms had shown little progression. The disease was believed by his father, a physician, to have been in a state of remission during this period although the patient stated that the intention tremor and diplopia had been worse in the past two years. He had also noted urgency and incontinence of urine when not alert. For one week he had noted numbness over the lateral and posterior aspect of the right thigh. The patient had had curare injections and physiotherapy two years before, the latter he felt with benefit. He had had pain in the knees and wrists, worse on motion, for three years. The patient stated he had had measles three times, the last attack 20 years before. Tonsillectomy had been performed 24 years previously. He had had two attacks of mild diarrhea during the past five years. Appendectomy had been performed in 1932, hemorrhoidectomy in 1942. The patient stated that during the operation, under spinal anesthesia, he had had partial paralysis of respiration. He had been unconscious for five hours after a head injury in 1938. Family history was significant only in that the mother had arthritis.

Examination revealed a well developed, well nourished, euphoric white male who walked uncertainly on a wide base assisted with a cane. The speech was slurred and scanning in type. Temperature was 97 degrees, pulse 100, blood pressure 100/70, height 67¼ inches and weight 153 pounds. The pupils were dilated by a cycloplegic because of recent refraction for glasses. The eyes showed slight nystagmus at rest and marked nystagmus on lateral and upward gaze. There was a right esophoria. There was temporal pallor of the optic discs. There was moderate weakness of the left arm and hand and of the left leg. Intention tremor of the upper extremities was slight but was marked in the lower extremities. Check was poor and rebound exaggerated in the arms but these findings were less marked in the legs. The deep reflexes were generally exaggerated, the superficial abdominal and cremasteric reflexes were absent. Babiniski and Hoffman signs were absent. There was an area of hypalgesia over the lateral and posterior aspect of the right thigh.

The only other pertinent findings were that the nasal and pharyngeal mucosa were red. The sinuses were clear to transillumination.

Foreign protein injections subcutaneously were begun and continued at home twice weekly by his father. An increased postnasal discharge of clear mucus was noted after the seventh and eighth injections. When seen at this time, the general appearance was improved, the patient had no joint pains and the weight was 160 pounds. The patient felt more energetic and brighter mentally. He noted that he could fix his gaze on an object more quickly, the speech had improved, the left arm was stronger and he noted that he could oppose thumb

and fingertips easily without looking. He stated that he had noticed more difficulty in walking but believed this was due to increased speed. The area of hypalgesia on the thigh had not changed. The nasal mucosa was still red. Injections were continued. When seen two weeks later, the patient had had a "cold" for six days. He felt "more sure of himself" in walking. The gait was objectively improved. He had noted hesitation on urination for the past two weeks. The speech continued to improve. He had noted a foul discharge from the nose following the foreign protein injection one week previously. A therapeutic dose of bismuth was given intramuscularly along with a foreign protein injection subcutaneously. Three days later the "cold" was much improved but a cough continued. Bladder urgency had returned. One week later the nose and throat appeared healthy, a postnasal drip continued. A foreign protein injection was given and two weeks later patient stated that he had had no nasal symptoms since. The improvement noted after the first six weeks was sustained. The patient was observed for a recurrence. One month later the patient stated he had noted a feeling of apprehension for one week and that the gait had been more unsteady. He had noted a postnasal drip on the morning of the day seen. The weight had dropped to 154½ pounds. The right side of the pharynx was red. There was little objective change in the station and gait. Foreign protein injections were resumed. After three more injections, the throat appeared healthy, no postnasal drip was present and the weight was 157 pounds. It was noted at this time that the nystagmus was slow and pendular. When seen two weeks later there was no nystagmus. General and neurological improvement was sustained. Two weeks later there was no nystagmus, other signs of improvement were sustained and there was no evidence of recurrence of infection in the upper respiratory tract. The patient was lost at this point because his father feared he might have a reaction to further foreign protein injections.

Comment

In the treatment of diseases due to chronic infection, any method of therapy calculated to do less than eradicate the infection must be only palliative.

The reaction in rheumatic fever due to retention or "backing up" of secretions as illustrated by case 96 indicates that the treatment should not be driven against a non-draining focus. Aggravation of joint pains following foreign protein injections in rheumatoid arthritis, however, undoubtedly represents a focal joint reaction. Free drainage should be encouraged in some cases by mechanical or surgical means. Similarly, abscessed teeth or other poorly draining foci should be removed before beginning treatment. It is felt that these precepts should be followed when any serious systemic disease is present although the reaction due to retention of secretions in other diseases is not as spectacular as in rheumatic fever. Experience with case 96 reported here and with other cases seen since is felt to give a new interpretation to the observations of Bland and Jones (37) on the effect of foreign protein injection in some cases of rheumatic fever.

In obtaining a "biologic cure of chronic infection," all foci must be removed and although little has been said about dental abscesses, cervicitis and vaginitis, prostatitis, etc., attention has been paid to these conditions in the patients treated. Although a focal reaction occurs in patients with vaginitis as indicated by an increased vaginal discharge, foreign protein therapy has not been adequate to eradicate the infection and proper local therapy has also been given.

Kinsely (38) has suggested that sludging of blood in the vasa vasorum may be the cause of atherosclerosis. In any case blood sludging no doubt is an important factor in producing the symptoms of chronic infection. The reversibility of this phenomenon would explain the result obtained in the patient (case 101) with angina pectoris. Similarly, manifestations of blood sludging must be expected to return with an uncomplicated "cold" even when eliminated within a few days by proper treatment.

In cirrhosis or chronic hepatitis (case 82), it is not necessary to assume with Adami (39) that infection from the bowel is responsible. The continued destruction of protein or the development of deficiencies leading to cirrhosis may go on in the presence of infection acting at some remote site.

The use of a method of administration of foreign protein not contraindicated in hypertension offers a means of demonstrating the relation of focal infection to hypertension. Experience with case 104 indicates that a relation does exist and further experience in other individuals, not here reported, has been felt to confirm this relationship. However, in several patients (one with malignant hypertension), although the symptoms such as occipital headache, vertigo and nervousness usually ascribed to high blood pressure, were abolished with presumptive cure of the infection, the blood pressure did not come down. No doubt irreversible changes must be expected in patients with hypertension as well as in those with arthritis or multiple sclerosis.

The use of a method of administration of foreign protein therapy not contraindicated in pregnancy offers a means of demonstrating the relation between chronic focal infection and toxemia of pregnancy. In addition to the case reported, the treatment has been used in three other cases—one in the first trimester, one in the second and one in the third trimester of pregnancy. Three have already been delivered of normal infants.

The use of a feasible method of administration of foreign protein therapy which can be carried to a proper end-point offers an opportunity to confirm the suspicion expressed by Wilder (40) that not only are the complications of diabetes due to focal infection but that diabetes itself is due to focal infection. The use of the treatment also offers an opportunity to demonstrate the relation between chronic infection and many diseases in which a relationship has been suspected to exist by many from time to time. Among these are peptic ulcer (41), ulcerative colitis (42), pernicious anemia (43),

Parkinson's Disease (44) and the diseases of the connective tissue system (45) other than rheumatic fever. Many diseases undoubtedly represent major reactions to chronic infection and should be considered no more "sacred" as entities than the many minor reactions to chronic infection.

The problem of "colds" during and following treatment has been partially met by the use of bismuth in combination with a foreign protein injection.

The solution to the problem of the "hyporeactor" could no doubt be applied to the good and fair reactor as well. The variation in reactions of some individuals from week to week suggests that the refractory state is reversible. During the summer months, the problem of the "hyporeactor" became more acute and many individuals whose reaction always fell short of presumptive cure were advised to return during the cold weather. Although, even during the summer, there were those in whom a presumptive cure was obtained in five or six injections of foreign protein, the number of injections given was usually greater than in the winter months. The summer weather in the Allegheny Valley simulates that of the lowland tropics. Sundstroem (46) has shown that there is a tendency to alkalosis under such conditions and that the basal metabolism is lowered. Ammonium chloride and hydrochloric acid in therapeutic doses given to a small number of patients did not appear to affect the reactions to foreign protein. Thyroid gland was given to a few patients but the use of this substance was not pursued since even a mild state of hyperthyroidism is an unpleasant, and in many persons, a dangerous state. Desoxycorticosterone acetate (47) in oil in five and 10 mg. doses intramuscularly at the time of the foreign protein injections was given to a few patients. There was no appreciable effect on the foreign protein reaction.

The result of further studies on this problem will be reported later.

Summary

1. Reference is made to a number of chronic diseases in which chronic infection has been incriminated as the etiologic agent.
2. The physiological and immunological effects of foreign protein therapy are reviewed.
3. A simple, relatively safe, and effective method of administration of foreign protein therapy is presented.
4. The results of treatment of a series of 114 cases with chronic infections of the upper respiratory tract are reported.
5. The relation of many disease "entities" to chronic infection is discussed.
6. A method of treatment of the common "cold" is presented also.

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BOOK REVIEWS

New Gould Medical Dictionary, by Blakiston, 1949, edited by Harold Wellington Jones, M.D., Normand L. Hoerr, M.D. and Arthur Osol, Ph.D.

Blakiston's New Gould Medical Dictionary is a completely new reference work. Working outward from the framework of Gould's Medical Dictionary, Fifth Edition, they have diligently searched recent professional literature not only for new terms but also for evidence of the changes in usage which they felt were evident today and so inadequately recorded in older reference works. The users of this dictionary will readily recognize the advantages of this broad investigation. In the field of pharmacology, for example, he will find that drugs described in the Pharmacopoeia of the United States of America, Thirteenth Revision (1947) in the National Formulary, Eighth Edition (1940) and in New and Nonofficial Remedies (1948) have, as a matter of course been defined, as have those other drugs in the United States Dispensatory, Twenty-fourth Edition (1947) and in various listings of medicinals bearing trade-marked proprietary, or other trade names which have sufficient use to be of reference interest. In so far as possible, drugs in various stages of animal and clinical investigation about which reports have been available were also defined.

The recognition of usage as the determining factor in the selection and treatment of the material greatly facilitated the solution of such vexing problems as that of handling conflicting and overlapping systems of terminology. In anatomy, for example, it has been possible to include not only the BNA (Basic Nomina Anatomica) terms and those BR (British Revision) terms which differ significantly from them, but also to retain that part of the old terminology (OT) which still remains in current clinical usage. Similarly, the fullest and most satisfactory coverage of various systems of nomenclature has been feasible in chemistry, bacteriology, psychiatry and many other fields in which conflicts exist.

The illustrative material has been treated as a functional part of the dictionary and by a system of keyed cross-references, integrated with it. This material has been as carefully selected and as thoroughly checked as the definitions. The terminology employed in labeling each structure shown conforms to the primary definition as given in the text. The virtues of the systematic arrangement of the illustrative plates and the advantages of presenting illustrations in sufficiently large units to indicate interrelationships will be readily evident to the user of the dictionary.

Etymology is properly considered an extension of and supplement to the definition, and within the limits of extreme brevity necessarily imposed upon the etymologic entries, every effort has been made to combine historical accuracy with usefulness. Since a knowledge of Greek is today seldom required even of medical students, full use can be assured only by adopting as the Editors have, a system for transliterating Greek into Roman characters. For the few who may desire to trace root words further in their Greek forms, a table of transliterations is provided.

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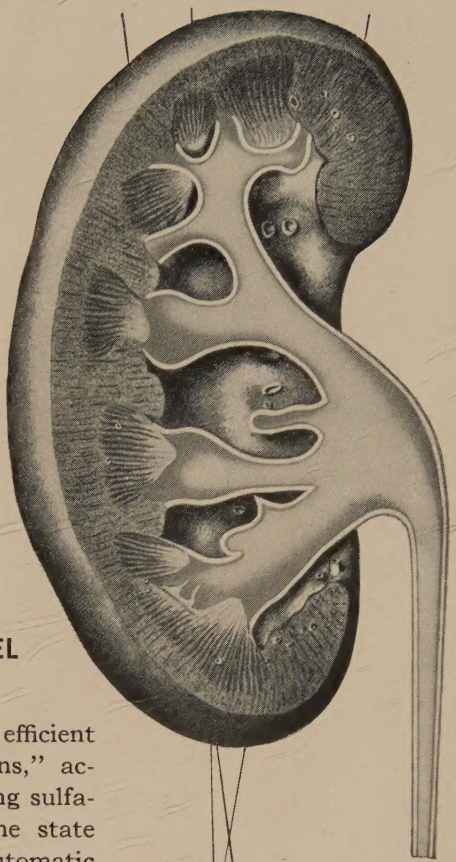

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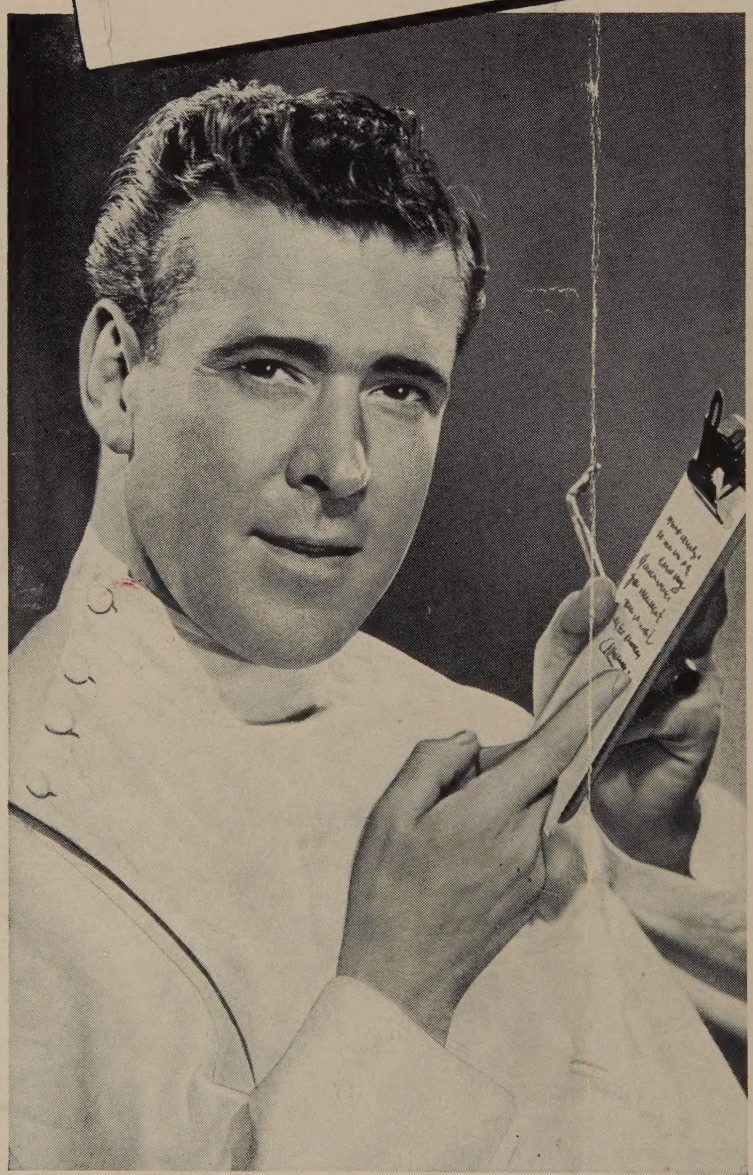

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